Remarks

The Office Action mailed March 17, 2010, has been received and reviewed. Claims 1-4, 6-8, 14, 17-21, 26, 29, 33, 41, 47, and 48 having been amended, and claim 52having been added, the pending claims are claims 1-4, 6-8, 14-24, 26-35, 41-43, and 47-53. Reconsideration and withdrawal of the rejections are respectfully requested.

An Interview was conducted on March 10, 2010, between Examiner Bao Li, Supervisor Patrick Nolan and Applicant's Representative David Provence. The statements provided by the Examiner in the interview summary, mailed March 17, 2010, form a complete and accurate record of this interview. The two rejections under §112, first and second paragraph were discussed. No agreement was reached.

In view of the interview, the independent claims have been amended to delete "90%" and replace with "95%."

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner has maintained the rejection of claims 1-5, 6-8, 14-24, 26-31, 33-35, 41-43, and 47-52 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The traversal of this rejection is respectfully maintained. In addition to remarks made in the replies dated June 9, 2009, and March 17, 2010, consideration of the following is requested.

The independent claims have been amended to recite "wherein the polyprotein comprises an amino acid sequence having at least about 95% identity to SEQ ID NO:2." It is Applicant's understanding that this addresses the Examiner's statement at paragraph 9 that "SEQ ID NO:2 is not cited in any o[f] the independent claims."

The Examiner asserts that the claims are confusing because they "do not define to which the 90% identity is compared" (paragraph 11 of the Office Action). The independent claims now recite "a first coding sequence . . . encoding a hepatitis C virus polyprotein, wherein the polyprotein comprises an amino acid sequence having at least about 95% identity to SEQ ID NO:2." A person of ordinary skill would recognize that the amino acid sequence of the polyprotein recited in the claims is compared to the amino acid sequence disclosed at SEQ ID NO:2.

Even if this were not readily recognized by a person of ordinary skill, this would be clear in view of the disclosure. The specification teaches that the present invention includes replication competent polynucleotides encoding an HCV polyprotein having similarity with the amino acid sequence of SEQ ID NO:2 (specification at page 17, lines 21-23), and the amino acid sequence of SEQ ID NO:2 is disclosed as being an HCV polyprotein (see page 19, lines 22-24). Moreover, SEQ ID NO:2 is from HCV strain H77 (page 11, lines 23-24), and strain H77 is a genotype 1a HCV (page 8, line 1). Thus, a person of skill in the art can readily understand that the amino acid sequence of the polyprotein recited in the claims is compared to the amino acid sequence disclosed at SEQ ID NO:2.

The Examiner asserts that the claims are confusing because they do not limit the polyprotein to having any of the mutations cited in the claims (paragraph 11 of the Office Action). The independent claims have been amended to recite

> "wherein the polyprotein comprises an amino acid sequence having at least about 95% identity to SEQ ID NO:2, and wherein the amino acid sequence of the polyprotein comprises at least three adaptive mutations, wherein the adaptive mutations comprise an isoleucine at about amino acid 2204 and at least two adaptive mutations selected from [6 different specifically defined residues]."

A person of ordinary skill would recognize that the polyprotein recited in the claims includes at least three adaptive mutations: an isoleucine at about amino acid 2204 and also at least two of the other recited adaptive mutations.

Reconsideration and withdrawal of the present rejections is respectfully requested.

The 35 U.S.C. §112, First Paragraph, Rejection

The Examiner has also maintained the rejection of claims 1-5, 6-8, 14-24, 26-31, 33-35, 41-43, and 47-52 under 35 U.S.C. 112, first paragraph, alleging the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention commensurate in scope with these claims. The traversal of this rejection is respectfully maintained. In addition to remarks made in the reply dated March 17, 2010, consideration of the following is requested.

At paragraph 24 of the Office Action, the Examiner appears to suggest the Applicant must provide certainty regarding which point mutations are important for maintaining or increasing replication competency of an HCV replicon ("the problem for *assuring* a HCV

replicon being able to replicate competently with a point mutation had not been solve[d] by the time when the Application was filed") (paragraph 24 of the Office Action, emphasis added). This is not the correct standard to use when evaluating whether a specification enables the claimed invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? The enablement requirement of §112 is satisfied when an application describes a claimed invention in a manner that permits one of ordinary skill to practice it, without undue experimentation. (MPEP § 2164.01). The specific question of whether experimentation is "undue" is determined based on the following eight Wands factors: 1. breadth of the claims; 2. nature of the invention; 3. state of the prior art; 4. level of ordinary skill in the art; 5. predictability of the art; 6. amount of direction provided in the specification; 7. any working examples; and 8. quantity of experimentation needed relative to the disclosure. (MPEP § 2164.01(a), citing In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

The claims are directed to isolated polynucleotides that include a 5'non-translated region (NTR), a 3' NTR, and a coding sequence located between the 5' and 3' NTRs. The coding sequence encodes a hepatitis C virus polyprotein comprising an amino acid sequence having at least about 95% identity to SEQ ID NO:2. The polyprotein encoded by the claimed coding sequence includes at least three adaptive mutations. One adaptive mutation is an isoleucine at about amino acid 2204. The other two adaptive mutations are chosen from six other adaptive mutations recited in the claims. The claimed isolated polynucleotides have the activity of being replication competent. Thus, the claims encompass a polynucleotide having a 5' and 3' NTR and a coding sequence encoding a protein with a minimum 95% identity with SEQ ID NO:2, and at least three adaptive mutations: an isoleucine at about amino acid 2204 and at least two of the other recited adaptive mutations. The claims also impose the function of requiring the polynucleotides to be replication competent.

It is submitted that the level of ordinary skill in the relevant art, the scope of which does not appear to be addressed in the Office Action, is relatively high.

Regarding the state of the prior art and the unpredictability of the art, in 1991 one of the first reports of a HCV genome found there were three regions of the HCV polyprotein that

shared amino acid sequence homologies with other viruses (Choo et al., 1991, 88:2451-2455). One region contained many residues in common with the putative NTP-binding helicases encoded by certain human, animal, and plant viruses, a second region contained the 6 residues highly conserved among all viral-encoded RNA-dependent RNA polymerases, and a third region immediately upstream of the putative NTP-binding helicase region contained those amino acids conserved among the putative trypsin-like serine proteases hypothesized to be encoded by certain viruses (Choo, paragraph spanning pages 2451 and 2454). More information on the presence and absence of conserved areas was also known at the filing date of the present application. For instance, the nucleotide sequences of many genotype 1a HCV were known as of the December 1, 2003, priority date for this patent application, and comparisons of sequence variation between different HCV were available to the public. Moreover, the crystal structures of some HCV proteins were also known at the priority date. Thus, the skilled person would have known which nucleotides and/or amino acids were conserved, and could readily predict whether mutation of a nucleotide would be expected to affect replication.

Moreover, the document cited by the Examiner, i.e., Cheney et al. (Virology, 287:298-306, 2002), is relevant when considering the the state of the prior art and the unpredictability of the art. Cheney et al. clearly shows that the production of mutations in a polyprotein and assaying for replication competency of the resulting polynucleotide is routine.

The Examiner makes the point that that results of a mutation on *in vitro* activity do not necessarily correlate with the effect of the mutation on *in vivo* replication of a virus. In Cheney et al. the truncation of four or eight amino acids from the conserved β-hairpin of NS5B protein resulted in enhanced activity as measured by two *in vitro* assays of NS5B activity; but these truncations resulted in loss of the ability to replicate in Huh-7 cells (see, for instance, Cheney at page 304, col. 1, third paragraph). It is respectfully submitted that the varying effect of mutations on *in vitro* and *in vivo* activity is irrelevant because the claims recite replication competent HCV replicons, and replication of a virus is known to occur within a cell. The claims do not refer to the *in vitro* activity of individual proteins encoded by the polyprotein.

Cheney et al. also describe other consensus sequence motifs or residues in NS5B, and they modify each of these and evaluate the effect of the mutations on replication competency. With four of the conserved residues, the authors note that the results "confirm[] the essential functions of these motifs or residues" (Cheney at page 304, col. 1, second paragraph). A fifth

conserved residue (arginine at position 345) was changed to a conservative lysine residue and resulted in increased replication (Cheney at page 304, col. 2, second paragraph). Taken together, the results of Cheney et al. show that mutations in conserved motifs resulted in changes in replication competency.

The specification also provides direction and guidance on making and using the claimed isolated polynucleotides. Further teaching on how to assay a polynucleotide for replication competency is disclosed at page 28, lines 3-23, and page 30, line 33 through page 32, line 24, where methods such as replication in a cultured cell and replication in an animal are taught. The specification also teaches how to identify the location of the claimed adaptive mutations. See the specification at, for instance, page 14, line 8 through page 16, line 9. For example, the location of the adaptive mutation at about amino acid 2204 can be determined by locating the amino acid sequence SSSA beginning at about amino acid 2200, where the amino acid immediately following the SSSA sequence is an isoleucine. Other landmarks are provided for the other six claimed adaptive mutations. Thus, the quantity of experimentation needed relative to the disclosure is low.

The Federal Circuit has repeatedly stated that enablement is not precluded by the necessity for some experimentation, so long as the experimentation needed to practice the invention is not undue, and that a considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance on how the experimentation should proceed. *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976), *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). In the present application, the quantity of experimentation required to practice the claimed invention amounts to two steps: (1) generating a polynucleotide comprising a coding sequence encoding a protein with a minimum 95% identity with SEQ ID NO:2, and having at least three adaptive mutations chosen from an isoleucine at about amino acid 2204 and at least two of the other recited adaptive mutations; and (2) assaying the polynucleotide for replication. See, for example, the working example at page 48, line 23 through page 50, line 7. The working example teaches methods for making generating a polynucleotide and assaying the replication competency of the polynucleotide.

For at least these reasons, reconsideration and withdrawal of the present rejection is respectfully requested.

Summary

It is respectfully submitted that the pending are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives at the telephone number listed below if it is believed that prosecution of this application may be assisted thereby.

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